

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 0 653 427 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
23.01.2002 Bulletin 2002/04

(51) Int Cl.7: **C07D 491/06, A61K 31/55**
// (C07D491/06, 307:00,
223:00)

(21) Application number: **94115959.2**

(22) Date of filing: **10.10.1994**

(54) **Galanthamine derivatives, a process for their preparation and their use as medicaments**

Galanthamin Derivate, ein Verfahren zu ihrer Herstellung und ihre Verwendung als Medikamente

Dérivés de la galanthamine, procédé pour leur préparation et utilisation comme médicaments

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT
SE**

(30) Priority: **15.10.1993 US 137440**

(43) Date of publication of application:
17.05.1995 Bulletin 1995/20

(60) Divisional application:
00107570.4 / 1 020 470

(73) Proprietor: **AVENTIS PHARMACEUTICALS INC.**
Cincinnati OH 45215-6300 (US)

(72) Inventors:
• **Kosley, Raymond W., Jr.**
Bridgewater, NJ 08807 (US)
• **Davis, Larry**
Sergeantsville, NJ 08557 (US)
• **Taberna, Veronica**
Union, NJ 07083 (US)

(74) Representative: **Wein, Elmar Michael et al**
**Aventis Pharma Deutschland GmbH, Patent- und
Lizenzabteilung**
65926 Frankfurt am Main (DE)

(56) References cited:
EP-A- 0 236 684 EP-A- 0 535 645
WO-A-88/08708 WO-A-92/20327

- **CHEMICAL ABSTRACTS, vol. 112, no. 13, 26**
March 1990, Columbus, Ohio, US; abstract no.
112096y, & NL-A-8 800 350 (STICHTING
BIOMEDICAL RESEARCH AND ADVICE GROUP)
- **THE MERCK INDEX 10TH EDITION, MERCK &**
CO., INC., 1983 RAHWAY, N.J., U.S.A. * No. 4210

Remarks:

The file contains technical information submitted
after the application was filed and not included in this
specification

EP 0 653 427 B1

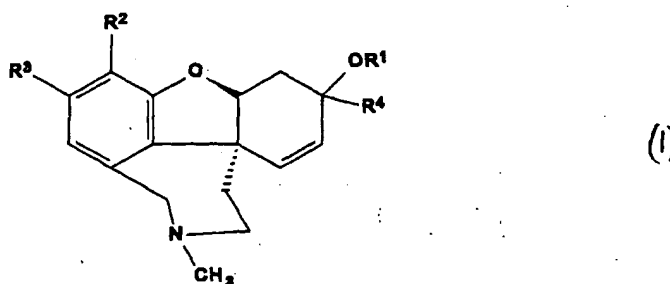
Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

[0001] The present invention relates to galanthamine derivatives, a process for their preparation and their use as medicaments.

[0002] WO 88/08708 discloses galanthamine derivatives such as 6-O-demethylgalanthamine and 6-methylaminocarbonyl-6-O-demethylgalanthamine for the inhibition of acetylcholinesterase and useful in the treatment of Alzheimer's disease.

[0003] This invention relates to compounds of the formula (I)



wherein

R¹ is hydrogen, (C₁-C₁₂)alkylcarbonyl, (C₁-C₁₂)alkoxycarbonyl, mono(C₁-C₁₂)alkylaminocarbonyl or di(C₁-C₈)alkylaminocarbonyl;

R² is monocyclic or multiple ring (C₃-C₁₂)cycloalkylcarbonyloxy or monocyclic or multiple ring (C₃-C₁₂)cycloalkyl (C₁-C₁₂)-alkylcarbonyloxy;

R³ is hydrogen, halo or (C₁-C₄)alkyl;

R⁴ is hydrogen or (C₁-C₆)alkyl;

all geometric, and optical and stereoisomers thereof, or a pharmaceutically acceptable addition salt thereof; which are useful for alleviating various memory dysfunctions such as found in Alzheimer's disease.

[0004] This invention also provides a pharmaceutical composition useful for alleviating various memory dysfunctions characterized by decreased cholinergic function which comprises a compound of the invention in an amount sufficient to affect cholinergic function and a pharmaceutically acceptable carrier.

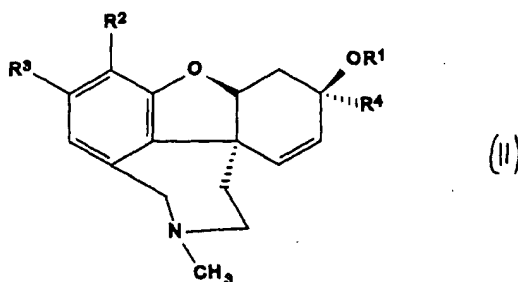
[0005] Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and appended claims.

[0006] The term "alkyl" shall mean a straight or branched alkyl group of the stated number of carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, sec-butyl, t-butyl, and straight and branched chain pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and dodecyl.

[0007] The term "halo" shall mean chloro, fluoro, bromo and iodo.

[0008] The term "cycloalkyl" shall mean a cycloalkyl group of from 3 to 12 carbon atoms such as for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclododecyl and including multiple ring alkyls such as for example, norbornanyl, adamantyl, cis-bicyclo[3.3.0]octanyl, camphoryl, and 3-noradamantyl.

[0009] In a preferred embodiment are compounds of the formula (II)



wherein

R¹ is hydrogen, (C₁-C₁₂)alkylcarbonyl, (C₁-C₁₂)alkoxycarbonyl;

R² is monocyclic or multiple ring (C₃-C₁₂)cycloalkylcarbonyloxy or monocyclic or multiple ring (C₃-C₁₂)cycloalkyl-(C₁-C₁₂)alkylcarbonyloxy;

R³ is hydrogen or halo;

R⁴ is hydrogen or (C₁-C₆)alkyl;

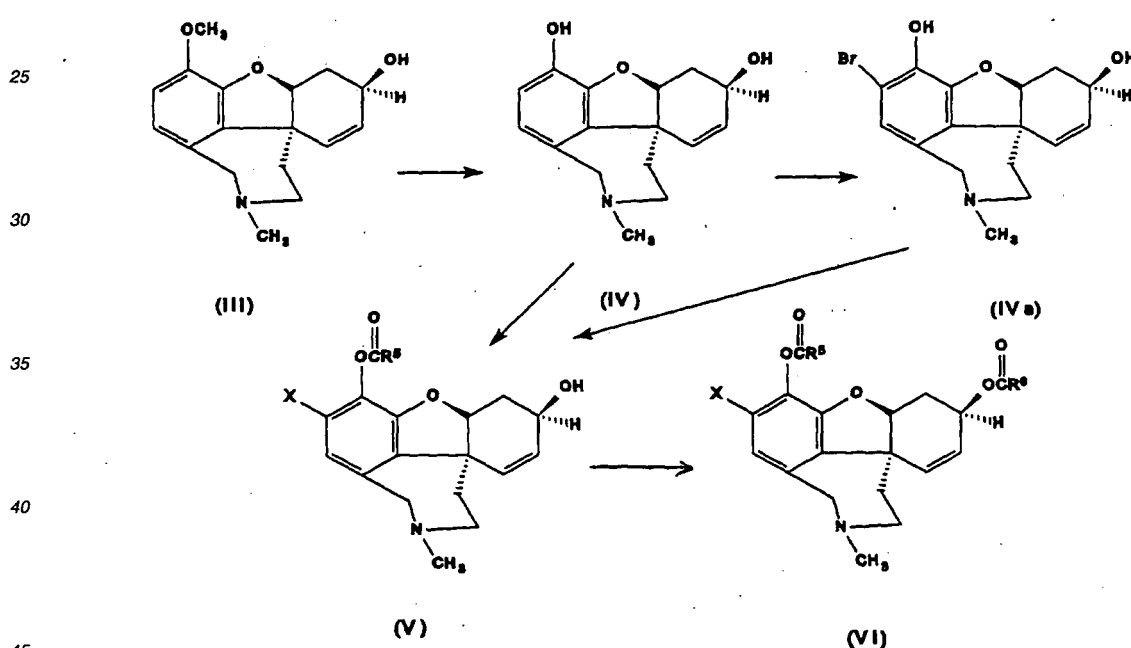
and all geometric, optical and stereoisomers and pharmaceutically acceptable addition salts thereof.

[0010] More preferably R¹ is hydrogen, (C₁-C₁₂)alkylcarbonyl or (C₁-C₁₂)alkoxycarbonyl; R² is monocyclic or multiple ring (C₃-C₁₂)cycloalkylcarbonyloxy or monocyclic or multiple ring (C₃-C₁₂)cycloalkyl-(C₁-C₁₂)alkylcarbonyloxy; R³ is hydrogen or bromine; and R⁴ is hydrogen or methyl.

[0011] Most preferably R¹ is hydrogen, R² is cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclohexylcarbonyloxy, methylcyclohexylcarbonyloxy, adamantylcarbonyloxy or adamantylmethylcarbonyloxy; and R³ and R⁴ are hydrogen.

[0012] The compounds of the invention are prepared from the appropriate optical isomer of galanthamine as described more fully below and shown in Scheme I.

SCHEME I



[0013] The intermediate 6-demethylgalanthamine of Formula IV, a known compound was prepared in a novel process by treating the galanthamine of Formula III with an alkylthio salt of sodium, potassium, lithium or cesium, preferably (C₁-C₄)alkylthio salts of sodium and lithium, most preferably EtSLi, or EtSNa. The reaction is typically carried out in a polar nonprotic solvent such as dimethylformamide (DMF) or N-methylpyrrolidone (NMP) or a protic solvent such as butanol or pentanol, preferably DMF or NMP at from about 80°C to about 135°C, preferably from about 90°C to about 125°C.

[0014] In the case where R⁵ is cycloalkyl, the compound of Formula IV is typically reacted with an appropriate carboxylic anhydride in the presence of a base such as 4-dimethylaminopyridine (DMAP) or carboxylic acid chloride in the presence of a base such as 1,8-diaza-biscyclo[5.4.0]undec-7-ene (DBU). The reactions are typically carried out in a non-protic solvent such as, for example, chloroform at from about 0°C to about 50°C, preferably from about 15°C to

about 30°C.

[0015] The compound of Formula VI can be prepared from the compound of Formula V. In the case where R⁶ is alkylamino, a solution of the appropriate isocyanate and the compound V in a nonprotic solvent such as tetrahydrofuran in a sealed tube at from about 55°C to about 85°C for from about 24 hours to about 120 hours, preferably at from about 60°C to about 70°C for from about 60 hours to about 80 hours.

[0016] In the case where R⁶ is alkyl, the compound of Formula V is reacted with the appropriate carboxylic acid or anhydride under the conditions described above to obtain the compound of Formula VI.

[0017] In the case where X is Br, the compound of Formula IV is treated with bromine in the presence of an amine such as t-butylamine to obtain the brominated compound. The bromine is first added to the t-butylamine at from about -20°C to about -30°C, then the reaction mixture is cooled to about -80°C to about -70°C and the galanthamine compound is added. The reaction is typically carried out in a nonpolar organic solvent such as for example toluene. Following addition of galanthamine the mixture is allowed to warm from about -80°C to about room temperature over from about 6 hours to about 10 hours, preferably about 8 hours.

[0018] In the case where R² of Formula I is hydrogen, the haloalkylsulfonyl compound of Formula V is typically reacted with palladium acetate and triphenylphosphine followed by triethylamine and formic acid. The reaction is typically carried out in a polar solvent such as dimethylformamide at from about room temperature to about 100°C, at about 60°C to about 70°C.

[0019] In the case where R⁴ of Formula I is alkyl, typically the appropriate narwedine compound is reacted with the appropriate alkylmagnesium bromide in the presence of cerium (III) chloride. The reaction is typically carried in a non-protic solvent such as tetrahydrofuran at from about -10°C to about room temperature, preferably at about 0°C.

[0020] The compounds of Formula I of the present invention can be used for the treatment of various memory dysfunctions characterized by decreased cholinergic function, such as Alzheimer's disease. The compounds of the present invention are advantageous because they are less toxic and/or more potent than the related compounds known in the art. In addition, the 6-O-demethyl ester and carbonate derivatives of this invention can cleave to yield 6-O-demethyl-galanthamine, a known acetylcholinesterase inhibitor.

[0021] This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and thereby increase acetylcholine levels in the brain.

[0022] The ability to inhibit acetylcholinesterase was determined by the photometric method of Ellman et al., Biochem. Pharmacol. 7,88 (1961).

[0023] This utility can also be ascertained by determining the ability of these compounds to restore cholinergically deficient memory in the Dark Avoidance Assay. In this assay mice are tested for their ability to remember an unpleasant stimulus for a period of 24 hours. A mouse is placed in a chamber that contains a dark compartment; a strong incandescent light drives it to the dark compartment, where an electric shock is administered through metal plates on the floor. The animal is removed from the testing apparatus and tested again, 24 hours later, for the ability to remember the electric shock.

[0024] If scopolamine, an anticholinergic that is known to cause memory impairment, is administered before an animal's initial exposure to the test chamber, the animal re-enters the dark compartment shortly after being placed in the test chamber 24 hours later. This effect of scopolamine is blocked by an active test compounds, resulting in a greater interval before re-entry into the dark compartment.

[0025] Effective quantities of the compounds of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

[0026] Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

[0027] The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum and the like. These preparations should contain at least 0.5% of active compounds, but may be varied depending upon the particular form and may conveniently be between 5% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0 - 200 milligrams of active compound.

[0028] The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent

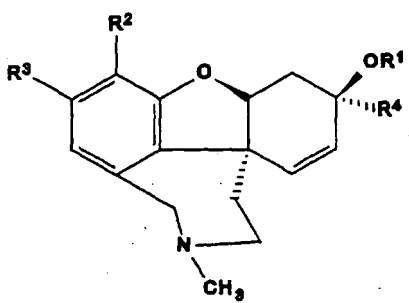
such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above-type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes, colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

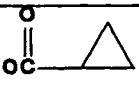

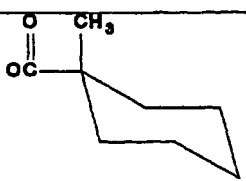
[0029] For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present inventions are prepared so that a parenteral dosage unit contains between 0.5 to 200 milligrams of active compound.

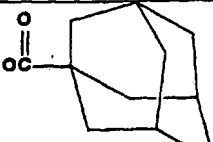
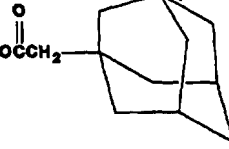
[0030] The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution; fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; anti-bacterial agents, such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral multiple dose vials may be of glass or plastic.

[0031] The following Table I and examples will further illustrate this invention. Examples 3 - 7 in Table I show typical compounds of the instant invention. The melting points are of hydrochloride salts unless otherwise indicated. Following Table I, representative illustrative preparations of compounds of the invention are described.

TABLE I



Ex. No.	R ¹	R ²	R ³	R ⁴	m.p. °C
1	H	OH	H	H	225-229° ^a
2	H	OH	Br	H	138-141°
3	H		H	H	244-245d
4	H		H	H	200-203
5	H		H	H	256-258d

6	H		H	H	258-260d
7	H		H	H	253-255
8	H	OCH ₃	H	CH ₃	237-240

* Lit. m.p. 220-222

* isolated as free base

REFERENCE EXAMPLE 1

6-O-Demethylgalanthamine

[0032] To a stirred solution of 20 ml of dry DMF at -40° C under nitrogen was added 0.57 ml (0.48 g) of ethanethiol. The mixture was stirred for several minutes at -40° to -30° C after which 2.84 ml of 2.5 M BuLi in hexanes was added slowly by syringe at -40° to -50° C. The solution was then allowed to warm to room temperature over 15 minutes, heated to 50° under aspirator vacuum and again cooled to 30° C. To the solution was added a solution of 0.57 g of galanthamine in 5.7 ml of dry DMF. The solution was stirred at 95-100° C for 2 hours and subsequently at 100-105° C for 3 hours, allowed to cool to room temperature and concentrated to an oil. The oil was dissolved in chloroform, shaken with NH₄Cl, made basic with aq NaHCO₃ and extracted four times with CHCl₃. The pH of the aqueous layer was then adjusted to 9-10 with NH₄OH and again extracted four times with chloroform. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to an oil. The oil was dissolved in degassed 5% methanol/chloroform and flash chromatographed on silica gel eluting with the same solvent system followed by 10% methanol/chloroform to provide a beige solid. The material was dissolved in acetone and allowed to crystallize overnight to provide 0.298 g of 6-O-demethylgalanthamine, m.p. 225-229° C.

ANALYSIS:

Calculated for C ₁₆ H ₁₉ NO ₃	70.31%C	7.01%H	5.12%N
Found	70.14%C	7.29%H	4.96%N

REFERENCE EXAMPLE 2

7-Bromo-6-O-demethylgalanthamine

[0033] To a stirred solution of 1.38 ml (0.966 g) of t-butylamine in 36 ml of azeotropically dried toluene at -20 to -30° C was added dropwise 0.34 ml (1.05 g) of bromine such that the temperature remained between -20 to -30° C. The solution was then cooled to -70 to -75° C and a solution of 3.0 g of 6-demethylgalanthamine in 15 ml of DMF was added slowly such that the temperature did not rise above -70° C. The solution was stirred for 2 hours at -70 to -78° C and subsequently allowed to warm slowly to room temperature over 6 hours. The solution was again cooled to 0° C, poured into ice/NaHCO₃/water, and extracted with chloroform. The aqueous fraction was saturated with NaCl and extracted 3 times with chloroform. The chloroform extracts were dried (Na₂SO₄), filtered and concentrated to an oil which was purified by HPLC, employing a Water Prep 500 Instrument and eluting with 3% methanol/chloroform, followed by 5% methanol/chloroform. The pure product-containing fractions were combined and concentrated to provide 1.83 g (47.3% based on 6-demethylgalanthamine, 78.9% based on bromine, the limiting reagent). Crystallization from acetone provided analytically pure 7-bromo-6-O-demethyl galanthamine, m.p. 138-141° C.

ANALYSIS:

Calculated for $C_{16}H_{18}BrNO_3$	54.56%C	5.15%H	3.98%N
Found	54.62%C	5.50%H	3.61%N

EXAMPLE 3

6-O-Demethyl-6-O-(cyclopropanecarbonyl)galanthamine hydrochloride

[0034] To a stirred mixture of 0.80 g (2.92 mmol) of 6-O-demethylgalanthamine in 8 ml of dry chloroform was added 0.44 ml (2.94 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The mixture was stirred at 0°C for 10 minutes after which was added 0.29 ml (3.19 mmol) of cyclopropanecarbonyl chloride by syringe. The mixture was warmed to room temperature and stirred at this temperature for 2 hours, poured into a cold saturated solution of sodium bicarbonate and extracted twice with chloroform. To the aqueous layer was added sodium chloride after which it was extracted twice with chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to provide a yellow oil. The oil was dissolved in chloroform, pipetted onto a flash chromatography column packed with silica gel and 3% methanol: chloroform and eluted with the same solvent system followed by 5% methanol: chloroform. The pure, product-containing fractions were combined and concentrated to provide 0.76 g (2.23 mmol, 76%) of a white solid. The solid was dissolved in diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 0.56 g (1.65 mmol; 56%) of 6-O-demethyl-6-O-(cyclopropanecarbonyl)galanthamine hydrochloride, m.p. 244-245°C (dec.).

ANALYSIS:

Calculated for $C_{20}H_{23}NO_4 \cdot HCl$	63.57%C	6.40%H	3.71%N
Found	63.29%C	6.39%H	3.74%N

EXAMPLE 4

6-O-Demethyl-6-O-(cyclobutanecarbonyl)galanthamine hemihydrate hydrochloride

[0035] To a stirred suspension of 1.00 g (3.66 mmol) of 6-O-demethylgalanthamine in 8.0 ml of dry chloroform was added 0.55 ml (3.67 mmol) of 1,8-diazabicyclo-[5.4.0]undec-7-ene. The suspension was stirred at 0°C for 10 minutes after which was added 0.47 g (4.00 mmol) of cyclobutanecarbonyl chloride. The reaction mixture was warmed to room temperature and stirred at this temperature for 3 hours after which it was poured into a cold, saturated solution of sodium bicarbonate. The mixture was extracted once with chloroform and the aqueous layer was treated with sodium chloride and extracted twice with chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to an oil. The oil was dissolved in chloroform and pipetted onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol: chloroform. The appropriate fractions were combined and concentrated to provide a solid weighing 0.71 g (1.77 mmol; 48%). The solid was dissolved in diethyl ether and chloroform and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to give 6-O-demethyl-6-O-(cyclobutanecarbonyl)galanthamine hemihydrate hydrochloride, m.p. 200-203°C.

ANALYSIS:

Calculated for $C_{21}H_{25}NO_4 \cdot 0.5H_2O \cdot HCl$	62.92%C	6.79%H	3.49%N
Found	62.68%C	6.84%H	3.43%N

EXAMPLE 5

6-O-Demethyl-6-O-(1-methylcyclohexanecarbonyl)galanthamine hydrochloride

[0036] To a stirred suspension of 0.37 g (2.63 mmol) of 1-methyl-1-cyclohexanecarboxylic acid in 1.0 ml of chloroform was added 0.54 g (2.61 mmol) of 1,3-dicyclohexylcarbodiimide dissolved in 1.0 ml of chloroform, followed by 0.71 g (2.62 mmol) of 6-O-demethylgalanthamine, and 3.17 g (2.59 mmol) of 4-dimethylaminopyridine dissolved in 1.5 ml of chloroform. The mixture was stirred at room temperature overnight after which it was poured into a cold saturated

solution of sodium bicarbonate and extracted twice with chloroform. To the aqueous layer was added sodium chloride after which it was extracted twice with chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to a yellow oil. The oil was dissolved in chloroform, filtered onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol:chloroform. The pure, product-containing fractions were combined and concentrated to a white solid weighing 0.49 g (1.25 mmol; 48%). The solid was dissolved in diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 6-O-demethyl-6-O-(1-methylcyclohexanecarbonyl)galanthamine hydrochloride, m.p. 256-258d.

ANALYSIS:			
Calculated for $C_{24}H_{31}NO_4 \cdot HCl$	66.42%C	7.43%H	3.23%N
Found	66.66%C	7.47%H	3.17%N

EXAMPLE 6

6-O-Demethyl-6-O-[(adamantan-1-yl)carbonyl]galanthamine hydrochloride

[0037] To a stirred solution of 0.59 g (3.28 mmol) of 1-adamantanecarboxylic acid in 1.5 ml of chloroform was added 0.68 g of 1,3-dicyclohexylcarbodiimide dissolved in 0.5 ml of chloroform, followed by 0.90 g (3.28 mmol) of 6-O-demethylgalanthamine, and 0.40 g of 4-dimethylaminopyridine dissolved in 0.5 ml of chloroform. The reaction mixture was allowed to stir at room temperature for 5 hours after which it was filtered onto a flash chromatography column, packed with silica gel and 3% methanol: chloroform and eluted with the same solvent system, followed by 5% methanol: chloroform. The pure, product-containing fractions were combined and concentrated to a white solid weighing 0.67 g (1.54 mmol; 47%). The solid was dissolved in chloroform and diluted with diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride. Recrystallization from acetonitrile:isopropanol followed by drying at 78°C, under high vacuum, provided 6-O-demethyl-6-O-[(adamantan-1-yl)carbonyl]galanthamine hydrochloride, m.p. 258-260°C (dec).

ANALYSIS:			
Calculated for $C_{27}H_{33}NO_4 \cdot HCl$	68.70%C	7.26%H	2.97%N
Found	68.46%C	7.48%H	2.87%N

EXAMPLE 7

6-O-Demethyl-6-O-[(adamantan-1-yl)methylcarbonyl]galanthamine hydrochloride

[0038] To a stirred suspension of 0.71 g (3.67 mmol) of 1-adamantaneacetic acid in 2.5 ml of chloroform was added 0.75 g (3.67 mmol) of 1,3-dicyclohexylcarbodiimide dissolved in 1.0 ml of chloroform, followed by 1.00 g (3.66 mmol) of 6-O-demethyl-galanthamine in 2.0 ml of chloroform and 0.45 g (3.67 mmol) of dimethylaminopyridine. The mixture was stirred for 2 hours after which it was filtered onto a flash chromatography column, packed with silica gel and 3% methanol:chloroform and eluted with the same solvent system, followed by 5% methanol:chloroform. The appropriate fractions were combined and concentrated to a white solid weighing 1.16 g (2.58 mmol; 70%). The solid was dissolved in diethyl ether and the hydrochloride salt precipitated by addition of ethereal hydrogen chloride to provide 0.90 g (1.86 mmol; 51%) of 6-O-demethyl-6-O-[(adamantan-1-yl)methylcarbonyl]galanthamine hydrochloride, m.p. 253-255°C (dec).

ANALYSIS:			
Calculated for $C_{28}H_{35}NO_4 \cdot HCl$	69.19%C	7.47%H	2.88%N
Found	68.93%C	7.51%H	2.85%N

REFERENCE EXAMPLE 8

3-(alpha-Methyl)galanthamine hydrochloride

[0039] Cerium (III)chloride (1.63 g, 6.63 mmol) was heated at 130-140°C for 2 hours then cooled and 22 ml of dry

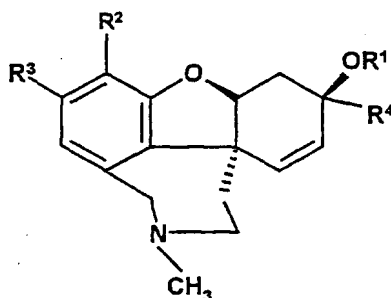
THF was added and the suspension was stirred overnight at room temperature. The suspension was then cooled in an ice/salt water bath and 2.2 ml of 3.0 M methyl magnesium bromide in diethyl ether was added. The mixture was stirred at ice bath temperature for 1.5 hours followed by the addition of a suspension of 1.25 g (4.39 mmol) of narwedine in 12.5 ml of THF. The resulting suspension was stirred for 0.5 hour and then poured into ice/ NH_4Cl /chloroform. The mixture was basified with sodium bicarbonate, extracted with chloroform, dried (Na_2SO_4), filtered and concentrated to provide 0.91 g of an oil. The oil was chromatographed by flash chromatography on silica gel eluting with chloroform followed by 2% methanol/chloroform/saturated ammonium hydroxide. The product containing fractions were combined and concentrated to provide 0.91 g of an oil. The oil was dissolved in ethyl acetate and flash chromatographed on silica gel, eluting with 2%, 5% and 10%, respectively, isopropyl alcohol/ethyl acetate (saturated ammonium hydroxide). The product containing fractions were combined and concentrated to provide an oil which was dissolved in ether, cooled and ethereal HCl was added. The suspension was filtered and the residue was washed with ether and dried for 2 hours at 80°C . The resulting solid was triturated with hot acetonitrile, centrifuge and dried to provide 0.20 g of product, m.p. $237-240^\circ\text{C}$.

ANALYSIS:

Calculated for $\text{C}_{18}\text{H}_{23}\text{NO}_3 \cdot \text{HCl}$	63.99% C	7.16% H	4.15% N
Found	63.83% C	7.15% H	4.00% N

Claims

1. A compound of the formula (II)



(II)

wherein

- R¹ is hydrogen, (C₁-C₁₂)alkylcarbonyl, (C₁-C₁₂)alkoxycarbonyl, mono(C₁-C₁₂)alkylaminocarbonyl or di(C₁-C₈)alkylaminocarbonyl;
 R² is monocyclic or multiple ring (C₃-C₁₂)cycloalkylcarbonyloxy or monocyclic or multiple ring (C₃-C₁₂)-cycloalkyl (C₁-C₁₂)-alkylcarbonyloxy;
 R³ is hydrogen, halo or (C₁-C₄)alkyl;
 R⁴ is hydrogen or (C₁-C₆)alkyl;

all geometric, and optical and stereoisomers thereof, or a pharmaceutically acceptable addition salt thereof.

2. A compound of the formula (II) as defined in claim 1, wherein

- R¹ is hydrogen, (C₁-C₁₂)alkylcarbonyl or (C₁-C₁₂)alkoxycarbonyl;
 R² is monocyclic or multiple ring (C₃-C₁₂)cycloalkylcarbonyloxy or monocyclic or multiple ring (C₃-C₁₂)cycloalkyl (C₁-C₁₂)alkylcarbonyloxy;
 R³ is hydrogen or halo;
 R⁴ is hydrogen or (C₁-C₆)alkyl;

and all geometric, optical and stereoisomers and pharmaceutically acceptable addition salts thereof.

3. A compound of the formula (II) as defined in claim 2,
wherein

R³ is hydrogen or bromine; and
R⁴ is hydrogen or methyl.

4. A compound of the formula (II) as defined in claim 3,
wherein

R¹ is hydrogen.

5. A compound of the formula (II) as defined in claim 4,
wherein

R³ and R⁴ are hydrogen.

6. A compound of the formula (II) as defined in claim 4,
wherein

R² is cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclohexylcarbonyloxy, methylcyclohexylcarbonyloxy, adamantylcarbonyloxy or adamantylmethylcarbonyloxy.

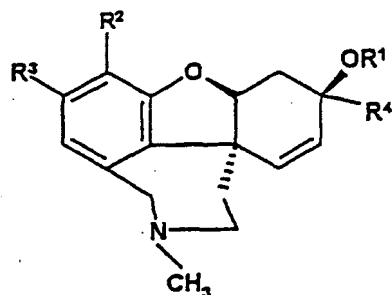
7. The compound of the formula (II) as defined in claim 1 or claim 2, which is (6-O-demethyl)-6-O[(adamantan-1-yl)-carbonyl]-galanthamine or a pharmaceutically acceptable acid addition salt thereof.

8. A pharmaceutical composition, which comprises a compound of the formula (II) as defined in claim 1 or claim 2 and a pharmaceutically acceptable acid addition salt thereof.

9. Use of the compound of the formula (II) as defined in claim 1 or claim 2 for the preparation of a medicament being useful for the treatment of memory dysfunction **characterized by** decreased cholinergic function.

Patentansprüche

1. Verbindung der Formel (II)



(II)

in welcher

R¹ für Wasserstoff, (C₁-C₁₂)-Alkylcarbonyl, (C₁-C₁₂)-Alkoxy carbonyl, Mono-(C₁-C₁₂)-alkylaminocarbonyl oder

- Di-(C₁-C₈)-alkylaminocarbonyl steht;
 R² ein monocyclisches oder polycyclisches (C₃-C₁₂)-Cycloalkylcarbonyloxy oder ein monocyclisches oder polycyclisches (C₃-C₁₂)-Cycloalkyl-(C₁-C₁₂)-alkylcarbonyloxy darstellt;
 R³ für Wasserstoff, Halogen oder (C₁-C₄)-Alkyl steht;
 5 R⁴ Wasserstoff oder (C₁-C₆)-Alkyl ist;

alle geometrischen und optischen und Stereoisomere davon, oder ein pharmazeutisch verträgliches Additionssalz davon.

10 **2.** Verbindung der Formel (II) gemäß Anspruch 1, in welcher

- R¹ für Wasserstoff, (C₁-C₁₂)-Alkylcarbonyl oder (C₁-C₁₂)-Alkoxy carbonyl steht;
 R² ein monocyclisches oder polycyclisches (C₃-C₁₂)-Cycloalkylcarbonyloxy oder ein monocyclisches oder polycyclisches (C₃-C₁₂)-Cycloalkyl-(C₁-C₁₂)-alkylcarbonyloxy darstellt;
 15 R³ für Wasserstoff, oder Halogen steht;
 R⁴ Wasserstoff oder (C₁-C₆)-Alkyl ist;

und alle geometrischen und optischen und Stereoisomere und pharmazeutisch verträglichen Additionssalze davon.

20 **3.** Verbindung der Formel (II) gemäß Anspruch 2, in welcher

- R³ für Wasserstoff oder Brom steht; und
 R⁴ Wasserstoff oder Methyl ist.

25 **4.** Verbindung der Formel (II) gemäß Anspruch 3, in welcher

- R¹ für Wasserstoff steht.

30 **5.** Verbindung der Formel (II) gemäß Anspruch 4, in welcher

- R³ und R⁴ für Wasserstoff stehen.

35 **6.** Verbindung der Formel (II) gemäß Anspruch 4, in welcher

- R² Cyclopropylcarbonyloxy, Cyclobutylcarbonyloxy, Cyclohexylcarbonyloxy, Methylcyclohexylcarbonyloxy, Adamantylcarbonyloxy oder Adamantylmethylcarbonyloxy ist.

40 **7.** Verbindung der Formel (II) gemäß Anspruch 1 oder 2, bei der es sich um (6-O-Demethyl)-6-O-[(adamant-1-yl)-carbonyl]galanthamin oder ein pharmazeutisch verträgliches Säureadditionssalz davon handelt.

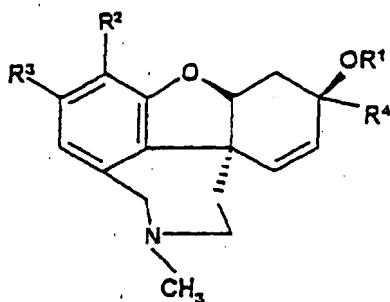
8. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (II) gemäß Anspruch 1 oder 2 und ein pharmazeutisch verträgliches Säureadditionssalz davon umfasst.

45 **9.** Verwendung der Verbindung der Formel (II) gemäß Anspruch 1 oder 2 für die Herstellung eines Arzneimittels, das sich für die Behandlungen von Gedächtnisstörungen eignet, die durch eine reduzierte cholinerge Funktion gekennzeichnet sind.

50 **Revendications**

1. Composé de formule (II)

55



(II)

dans lequel

R¹ représente un atome d'hydrogène, un groupe alkyl(en C₁ à C₁₂)carbonyle, alkoxy(en C₁ à C₁₂)carbonyle, monoalkyl(en C₁ à C₁₂)aminocarbonyle ou dialkyl(en C₁ à C₈)aminocarbonyle;
 R² représente un groupe cycloalkyl(en C₃ à C₁₂)carbonyloxy monocyclique ou polycyclique ou cycloalkyl(en C₃ à C₁₂)alkyl(en C₁ à C₁₂)carbonyloxy monocyclique ou polycyclique;
 R³ représente un atome d'hydrogène, d'halogène ou un groupe alkyle en en C₁ à C₄;
 R⁴ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆;
 tous ses isomères géométriques, optiques et ses stéréoisomères, ou
 un sel d'addition de celui-ci acceptable sur le plan pharmaceutique.

2. Composé de formule (II) selon la revendication 1, dans lequel

R¹ représente un atome d'hydrogène, un groupe alkyl(en C₁ à C₁₂)carbonyle ou alkoxy(en C₁ à C₁₂)carbonyle;
 R² est un groupe cycloalkyl(en C₃ à C₁₂)carbonyloxy monocyclique ou polycyclique ou cycloalkyl(en C₃ à C₁₂)alkyl(en C₁ à C₁₂)carbonyloxy monocyclique ou polycyclique;
 R³ représente un atome d'hydrogène ou d'halogène;
 R⁴ représente un atome d'hydrogène ou un groupe alkyle en C₁ à C₆;
 et tous ses isomères géométriques, optiques et ses stéréoisomères et ses sels d'addition acceptables sur le plan pharmaceutique.

3. Composé de formule (II) selon la revendication 2, dans lequel

R³ représente un atome d'hydrogène ou de brome; et
 R⁴ représente un atome d'hydrogène ou un groupe méthyle.

4. Composé de formule (II) selon la revendication 3, dans lequel
 R¹ est un atome d'hydrogène.

5. Composé de formule (II) selon la revendication 4, dans lequel
 R³ et R⁴ représentent un atome d'hydrogène.

6. Composé de formule (II) selon la revendication 4, dans lequel
 R² est un groupe cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclohexylcarbonyloxy, méthylcyclohexylcarbonyloxy, adamantylcarbonyloxy ou adamantylméthylcarbonyloxy.

7. Composé de formule (II) selon la revendication 1 ou 2, qui est 1a (6-O-déméthyl)-6-O[(adamantan-1-yl)carbonyl]-galanthamine ou un sel d'addition d'acide de celle-ci acceptable sur le plan pharmaceutique.

8. Composition pharmaceutique, qui comprend un composé de formule (II) selon la revendication 1 ou 2 et un sel d'addition d'acide de celui-ci acceptable sur le plan pharmaceutique.

9. Utilisation du composé de formule (II) selon la revendication 1 ou 2 pour la préparation d'un médicament étant

EP 0 653 427 B1

utile pour le traitement du dysfonctionnement de la mémoire **caractérisé par** une fonction cholinergique diminuée.

5

10

15

20

25

30

35

40

45

50

55